d_4^{30} 1.123 and $n^{20}D$ 1.4241; ir 5.73 (C=O), 8.13 (=COC), and 10.31 (oxetane ring).

Anal. Calcd for $C_5H_8O_3$: C, 51.7; H, 7.81. Found: C, 51.6; H, 7.92.

Oxetyl acetate was also prepared by acylation of oxetanol with acetyl chloride. Oxetanol (5.63 g, 76 mmol) in benzene (75 ml) containing Et_3N (7.70 g, 76 mmol) was treated at 0° with acetyl chloride (5.96 g, 76 mmol). After 30 min gc showed a conversion of 95%. The reaction mixture was extracted with 75 ml of water and the organic phase was washed three times with 10-ml portions of water. Analysis of the water extract after 2 days showed the presence of product, which was extracted with three 15-ml portions of benzene after saturation with salt. Some product was probably lost through hydrolysis in the aqueous phase. The combined organic layers were distilled at atmospheric pressure to remove solvent and the crude product was vacuum distilled through a 6-in. glass helices packed column to give oxetyl acetate (5.33 g, 46 mmol, 64% corrected yield), bp 46–47° (7 mm).

Oxetyl Acrylate.—3-Oxetanol (50.0 g, 0.68 mol), ethyl acrylate (134 g), aluminum isopropoxide (1.5 g), and phenyl-β-naphthylamine (3 g) were heated to reflux. Only a trace of ethanol was found in the distillate. Metallic sodium, (0.5 g) was added, and 100 ml of ethyl acrylate was distilled and replaced with 100 ml of allyl acrylate. The latter was slowly distilled and the residue was vacuum distilled, giving 3-oxetanol (34 g, 0.46 mol), a higher boiler [74–76° (1 Torr), 6 g], and 12 g of pot residue. The oxetanol fraction contained about 5% of a higher boiling material which was trapped by gc (125°, silicone column) and identified as oxetyl acrylate (6% yield) by ir.

Oxetyl acrylate was also prepared by reaction of oxetanol with acrylyl chloride. Oxetanol (5.63 g, 76 mmol) in benzene (75 ml) containing Et_3N (7.70 g, 76 mmol) was treated at 0° with acrylyl chloride (6.88 g, 76 mmol). Conversion after 30 min as determined by gc was about 95%. The reaction mixture was worked up as described under the preparation of oxetyl acetate. The distilled oxetyl acrylate [3.5 g, (27 mmol), 38% corrected yield] had the following physical properties: bp 58° (6.5 mm); d_4^{28} 1.111; $n^{20}D$ 1.4515; ir 5.81 (C=O), 6.13 and 6.18 (C=C), and 10.31 μ (oxetane ring).

Anal. Calcd for $C_6H_8O_3$: C, 56.2; H, 6.29. Found: C, 56.1; H, 6.14.

Ethyl 3-(3′-Oxetoxy)propionate.—The high-boiling fraction obtained in the preparation of oxetyl acrylate was identified by nmr as ethyl 3-(3′-oxetoxy)propionate (0.035 mol, 16% yield): d_4^{21} 1.090; $n^{21}D$ 1.4384; ir 5.77 (C=O), 8.45 (=COC), and 10.29 μ (oxetane ring).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.2; H, 8.10. Found: C, 55.1; H, 8.03.

Attempted Dehydroacetoxylation of Oxetyl Acetate.—In the first experiment oxetyl acetate (9.3 g, 0.08 mol) was passed in 7 min through a 30 × 1 cm Vycor tube at 490 ± 10°. Almost all of the oxetyl acetate was recovered unchanged. In a second run oxetyl acetate (8.1 g, 0.07 mol) was passed in 40 min through the reactor at 605 ± 5°. The condensate was collected in pyridine (14 g) cooled to −40°. This receiver was followed by a water condenser and a −78° trap. The condensate in the first receiver amounted to 6.3 g; nothing was collected in the −78° trap. Gc (Igepal column) and ir showed a small amount of H_2O and unchanged starting material.

Oxetyl acetate was heated in a sealed tube with excess diethylamine for several hours at 150°; no evidence of reaction was observed.

Polyoxetanol.—A freshly distilled sample of 3-oxetanol (about 150 g) became hazy after several weeks under ambient conditions and after a few months it had a milky appearance. Filtration and ether washing gave 0.6 g of white, amorphous powder, mp 125–130°, mol wt (osmometric), 1397. The milky filtrate was distilled (65°, 5 Torr) and the pot residue was dissolved in hot ethanol. On cooling an additional 1.5 g of precipitated polyoxetanol was obtained, mp 125–135°, mol wt, 1723. Both fractions of polyoxetanol were water soluble, ir (KBr) 2.97 (OH) and 8.99 μ (COC), nmr (DMSO-d_6) doublet centered at 4.66 ppm (sec OH).

Anal. Calcd for $(C_3H_6O_2)_x$: C, 48.6; H, 8.16. Found: C, 47.8; H, 8.2.

Registry No.—**1**, 6777-00-0; *cis*-**2**, 40307-01-5; *trans*-**2**, 40307-02-6; **4**, 7748-36-9; **4** polymer, 39275-61-1; **11**, 26272-83-3; **12**, 26272-86-6; **13**, 39267-79-3; **14**, 26272-85-5; **15**, 39267-81-7; **16**, 6704-31-0; **18**, 39267-83-9; **19**, 39267-84-0; **20**, 39267-85-1; tosyl chloride, 98-59-9; diethylamine hydriodide, 19833-78-4; 2,3-(diethylamino)propanol, 13429-30-6; 3-chlorooxetane, 4741-80-4; allyl acetate, 591-87-7; acetyl chloride, 75-36-5; ethyl acrylate, 140-88-5; acrylyl chloride, 814-68-6.

Acknowledgment.—The authors are indebted to Dr. R. C. Rittner, Mr. J. Culmo, and Mr. J. Giunta for microanalyses, and to Mr. G. D. Vickers and Dr. T. Groom for nmr analyses.

On the Mechanism of Alkaline Hydrolysis of Methylthiopurines[1]

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Received January 16, 1973

Di- and trimethylthiopurines, which can form anions, are resistant to alkaline hydrolysis. After introduction of an *N*-methyl substituent, these compounds are incapable of forming anions and become susceptible to attack by hydroxyl ion. The course of these reactions can be predicted satisfactorily by Fukui's superdelocalizabilities for nucleophilic attack; the same order of reactivities is derived for analogous methylthio- and chloropurines, in accordance with the limited experimental observations.

Many attempts have been made to establish the order of reactivity of purines toward nucleophilic reagents. The most useful model is 2,6,8-trichloropurine (TCP), in which nucleophilic displacement of the halogens by a variety of bases follows the order 6 > 2 > 8.[2-4] However, for 7- and 9-methyl-TCP, the relative reactivity toward ethoxide ion was found to be 8 > 6 > 2.[4,5] The latter result is in good agreement with the observations of Barlin[6] on the three isomeric 9-methylmonochloropurines and has been explained as follows.[5] The reaction of TCP with bases involves the anion of the substrate, in which the negative charge is concentrated mainly in the imidazole ring, thus making nucleophilic attack at C-8 difficult. The 7- or 9-methyl derivatives of TCP cannot form anions and thus follow the order of reactivity derived

(1) Dedicated to our teacher and friend, Professor E. Lederer, Director, Institut de Chimie des Substances Naturelles, Gif-Sur-Yvette, France, on the occasion of his 65th birthday.

(2) (a) E. Fischer, *Chem. Ber.*, **30**, 2226 (1897); (b) R. K. Robins and B. E. Christensen, *J. Amer. Chem. Soc.*, **74**, 3624 (1952).

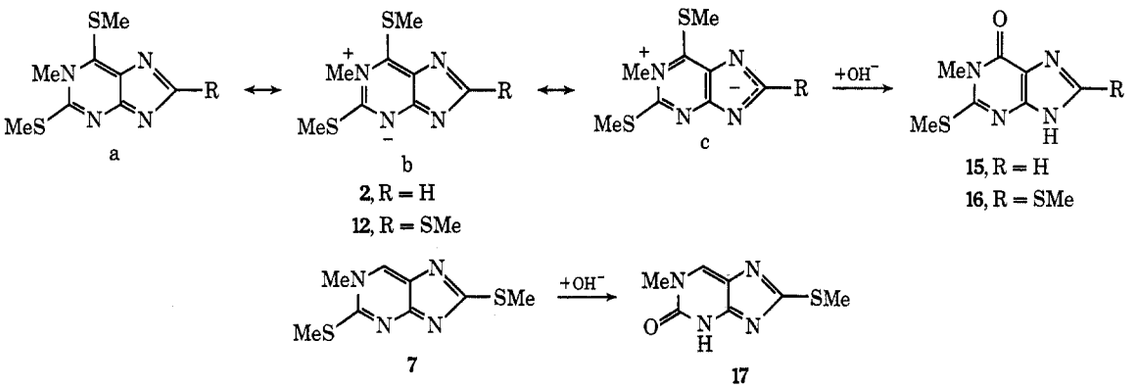
(3) S. R. Breshears, S. S. Wang, S. G. Bechtolt, and B. E. Christensen, *J. Amer. Chem. Soc.*, **81**, 3789 (1959).

(4) E. Fischer, *Chem. Ber.*, **30**, 1846 (1897).

(5) E. Y. Sutcliffe and R. K. Robins, *J. Org. Chem.*, **28**, 1662 (1963).

(6) G. B. Barlin, *J. Chem. Soc. B*, 954 (1967).

SCHEME I



by Mason[7] from MO calculations for the neutral form of purine.

We have reinvestigated this problem, using as a model the alkaline hydrolysis of di- and trimethylthiopurines. We shall demonstrate that the introduction of an *N*-methyl substituent has a decisive influence on the direction of nucleophilic attack, and shall derive a general scheme for these reactions.

The 2,6- (**1**), 2,8- (**6**), and 6,8-dimethylthiopurines (**8**) and likewise the trimethylthio derivative **11** proved to be resistant to hydrolysis by boiling 2 *N* sodium hydroxide. On the other hand, the corresponding 2,6-,[3] 6,8-,[8] and 2,8-dichloropurines,[9] like TCP, do react under these conditions. This we ascribe to the fact that chloride ion is a much better leaving group than the methylmercaptide ion.

In contrast, all *N*-methyl derivatives of the above methylthiopurines, being unable to form anions, undergo alkaline hydrolysis. The results are summarized in Table I.

TABLE I
HYDROLYSIS OF DI- AND TRIMETHYLTHIOPURINES BY NUCLEOPHILIC REAGENTS

No.	Compd	Attack at position	Method used[a]	Product
1	2,6-Dimethylthiopurine		E	
2	1-Methyl-2,6-dimethylthiopurine	6	A, B	15
3	3-Methyl-2,6-dimethylthiopurine	2	C	18
4	7-Methyl-2,6-dimethylthiopurine	6	D	23
5	9-Methyl-2,6-dimethylthiopurine	6	D	21
6	2,8-Dimethylthiopurine		E	
7	1-Methyl-2,8-dimethylthiopurine	2	D	17
8	6,8-Dimethylthiopurine		E	
9	3-Methyl-6-methylthio-8-chloropurine	6	$(SH^-)^b$	20
10	3-Methyl-6,8-dichloropurine	6	$(SH^-)^b$	20
11	2,6,8-Trimethylthiopurine		E	
12	1-Methyl-2,6,8-trimethylthiopurine	6	*c*	16
13	3-Methyl-2,6,8-trimethylthiopurine	2	C	19
14	9-Methyl-2,6,8-trimethylthiopurine	8	E	22

[a] For specification of the conditions used see Experimental Section. [b] With these purines, thiohydrolysis was tested instead of hydrolysis by OH^-. [c] **12** was so sensitive to hydrolysis that it could not be isolated in pure form.

1-Methyl-2,6-dimethylthiopurine (**2**) is hydrolyzed instantaneously by dilute ammonia at room temperature, or even by boiling water, at position 6 to yield the hypoxanthine **15** (Scheme I). The corresponding 1-methyl-2,6,8-trimethylthio derivative **12** is so sensitive to hydrolysis that it could not be isolated in pure form. Treatment of 1-methyl-2,8-dimethylthio-6-thiopurine (**31**, Scheme VI) with methyl iodide in DMF or acetonitrile, either at room temperature or at 70°, was ineffective. When the purine **31** was dissolved in dilute aqueous alkali and treated at room temperature with methyl iodide, the hypoxanthine **16** was obtained directly (Scheme VI). This result clearly demonstrates that in **12**, again, the 6-SMe group is the most reactive one (Scheme I).

If, however, the 6-methylthio substituent is missing, as in **7**, then alkali attacks at position 2 to give **17** (Scheme I). Combination of the results, obtained with **2**, **12**, and **7**, permits us to establish for 1-methyl-2,6,8-trimethylthiopurine (**12**) the following sequence of reactivity toward nucleophilic reagents: 6 > 2 > 8.

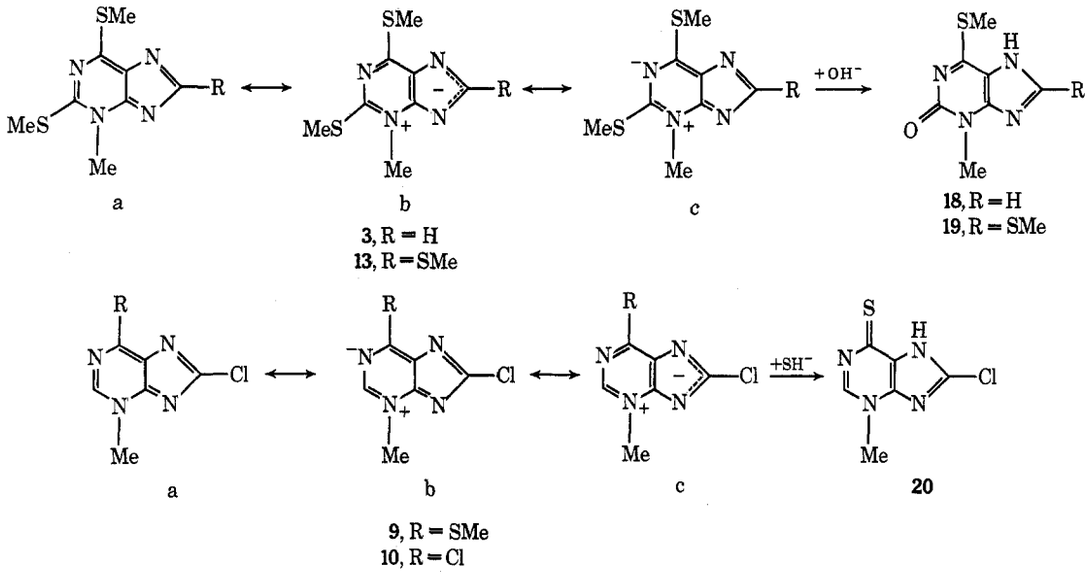
3-Methyl-2,6-dimethylthiopurine (**3**) and the corresponding trimethylthio derivative **13** both undergo hydrolysis at position 2 to yield **18** and **19**, respectively (Scheme II). In order to determine whether position 6 or 8 follows next on the reactivity scale, we should test 3-methyl-6,8-dimethylthiopurine. However, this compound decomposed rapidly in alkaline media, and no defined product could be isolated. Therefore results are based on observations with 3-methyl-6-methylthio-8-chloropurine (**9**), which was found previously to react with sulfhydryl ion at position 6 to give **20**,[10] although, as stated before, chloride ion is a much better leaving group than the methylmercaptide ion. In analogy, 3-methyl-6,8-dichloropurine (**10**) reacted with sulfhydryl ion first at position 6 to yield again **20**[10] (see Scheme II). On this basis, we may derive for 3-methyl-2,6,8-trimethylthiopurine (**13**) the sequence 2 > 6 > 8 for nucleophilic attack.

In 9-methyl-2,6,8-trimethylthiopurine (**14**), hydrolysis involves position 8 (**22**), while, in 9-methyl-2,6-dimethylthiopurine (**5**), position 6 is attacked first (**21**) (Scheme III). These results lead to the same order of reactivity as that established by Sutcliffe and Robins[5] for 9-methyl-TCP, *viz.*, 8 > 6 > 2.

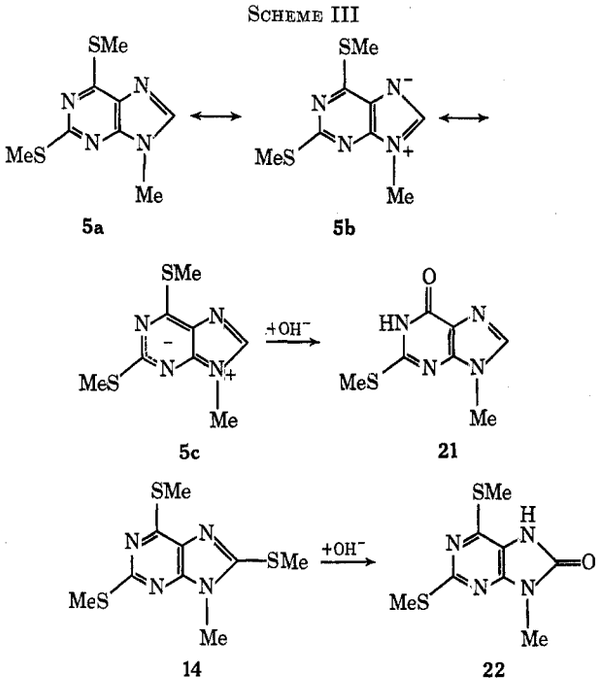
The 7-methyl derivative of **11** was not available. From the experiments with 7-methyl-TCP[5] and from our own observations with 7-methyl-2,6-dimethylthiopurine (**4**), which yielded the hypoxanthine **23** (Scheme IV), we suggest again the sequence 8 > 6 > 2.

(7) S. F. Mason in "The Chemistry and Biology of Purines," Ciba Foundation Symposia, 1957, p 72.
(8) R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 6671 (1958).
(9) A. G. Beaman and R. K. Robins, *J. Appl. Chem.*, **12**, 432 (1962).
(10) D. Diller, Z. Neiman, and F. Bergmann, *J. Chem. Soc. C*, 878 (1968).

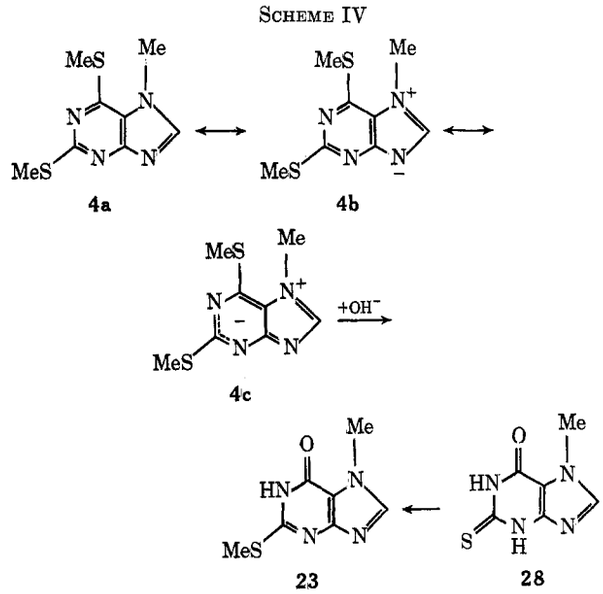
SCHEME II



SCHEME III



SCHEME IV



In Table I, we show also the various procedures used to split off the most reactive methylthio group in each case. Column 3 shows that the relative velocity for the various *N*-methyl derivatives is 1-Me ≫ 3-Me > 7-Me ~ 9-Me.

MO Calculations of Relative Susceptibility to Nucleophilic Attack.—Using Pullman's parametrization,[11] we have performed π-electronic Hückel-type calculations on methylthiopurines; the coefficients of the wave functions were subjected to a "frontier" analysis, as formulated by Fukui,[12] in order to obtain the superdelocalizabilities for nucleophilic attack. In these calculations, we have followed the same principle used above to determine the experimental sequences of reactivities. First, the site most susceptible to nucleophilic attack was derived for the isomeric *N*-methyl-2,6,8-trimethylthiopurines. Next, the susceptibility of the dimethylthiopurine, lacking the most reactive SMe substituent, was analyzed. The results in Table II (A) are in perfect agreement with the sequences found experimentally.

In a few cases (7- and 9-methyl-TCP,[5] 7-methyl-2,6-dichloropurine,[13] and **10**), the sequence of *N*-methylchloropurines for nucleophilic attack has been found identical with that established for the corresponding methylthio derivatives **4**, **5**, and **9**. Therefore we have also calculated the superdelocalizabilities for nucleophilic attack of *N*-methyldi- and -trichloropurines, following the principles explained above. Table II (B) not only shows agreement with the limited experimental data, but also predicts that, in this series, all sequences should be identical with those of the corresponding methylthiopurines.

(11) A. Pullman and B. Pullman, "Quantum Biochemistry," Interscience, New York, N. Y., 1963, p 108.

(12) K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.*, **20**, 722 (1952).

(13) R. N. Prasad and R. K. Robins, *J. Amer. Chem. Soc.*, **79**, 6401 (1957).

TABLE II

SEQUENCE OF NUCLEOPHILIC ATTACK, DERIVED FROM FUKUI'S SUPERDELOCALIZABILITIES[a]

Registry no.	Compd	Superdelocalizability for nucleophilic attack C-2	C-6	C-8	Sequence
	A. Methylthiopurines				
	1-Methyl-2,6,8-trimethylthiopurine (12)	0.898	*0.984*	0.846	6 > 2 > 8
	1-Methyl-2,8-dimethylthiopurine (7)	*0.896*		0.761	
	3-Methyl-2,6,8-trimethylthiopurine (13)	*0.825*	0.697	0.815	2 > 6 > 8
	3-Methyl-6,8-dimethylthiopurine		*0.877*	0.657	
	7-Methyl-2,6,8-trimethylthiopurine	0.720	0.724	*0.852*	8 > 6 > 2
	7-Methyl-2,6-dimethylthiopurine (4)	0.759	*0.795*		
	9-Methyl-2,6,8-trimethylthiopurine (14)	0.800	0.826	*0.889*	8 > 6 > 2
	9-Methyl-2,6-dimethylthiopurine (5)	0.773	*0.813*		
	B. Chloropurines				
39008-33-8	1-Methyl-2,6,8-trichloropurine	1.310	*1.865*	0.942	6 > 2 > 8
39008-34-9	1-Methyl-2,8-dichloropurine	*1.319*		0.963	
39008-35-0	3-Methyl-2,6,8-trichloropurine	*1.790*	1.763	0.974	2 > 6 > 8
18019-41-5	3-Methyl-6,8-dichloropurine		*1.793*	0.991	
16404-16-3	7-Methyl-2,6,8-trichloropurine	0.962	1.062	*1.283*	8 > 6 > 2
2273-93-0	7-Methyl-2,6-dichloropurine	0.963	*1.069*		
39008-39-4	9-Methyl-2,6,8-trichloropurine	0.997	1.104	*1.181*	8 > 6 > 2
2382-10-7	9-Methyl-2,6-dichloropurine	1.003	*1.113*		

[a] The most susceptible site in each derivative is italicized.

Discussion

In Fukui's method, the site most susceptible to nucleophilic attack is calculated. Resonance theory derives all possible polar forms of a heterocyclic molecule in its ground state, in most cases without any indication of their relative contributions. Moreover, the activation process during a chemical reaction may change these contributions in favor of one specific form. Nevertheless, we shall try in the following to discuss the probable course of the nucleophilic reactions of methylthiopurines in terms of resonance theory.

In the neutral molecules of **3**, **7**, **13**, and **14**, the methylthio group nearest to the *N*-methyl substituent is the first to suffer hydrolysis. Thus, in these cases, the attack of OH^- is clearly directed by the *N*-methyl group, presumably by virtue of its positive charge in the polarized molecule, as for instance in **3b** and **13b** (Scheme II). This type of electrostatic attraction is strongly enhanced during approach of the nucleophilic reagent; *i.e.*, **3b** and **13b** become predominant over **3c** and **13c**.

In the polarized forms of **2** and **12**, the negative charge is spread over position 3 (**2b** and **12b**) and the imidazole ring (**2c** and **12c**) (Scheme I). Thus, although the positive center at N-1 is at equal distance from the 2- and 6-methylthio substituents, the approach of OH^- to position 2 is less favored because of the adverse effect of the partial negative charge at N-3. Although mesomer c, in which the aromatic structure of the pyrimidine ring is preserved, probably makes a more important contribution, only mesomer b introduces a difference in the nucleophilicity of positions 2 and 6; thus attack at position 6 becomes predominant.

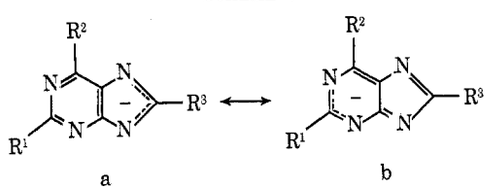
Similar considerations may be applied to those dimethylthiopurines in which hydrolysis of one SMe substituent is preferred, although the *N*-methyl group is not adjacent to any methylthio group. Thus, in the polarized forms of **9** and **10**, the negative charge is spread over N-1 (**9b**, **10b**) and the imidazole ring (**9c**, **10c**) (Scheme II). Here, mesomer c contributes more than the b form because of the aromatic structure of the pyrimidine ring in c and because of the participation of both N-7 and N-9 in the distribution of the negative charge. Mesomer c becomes even more predominant during the approach of the anion SH^-, so that thiohydrolysis of the 6 substituent in the pyrimidine moiety is preferred.

Similarly in the polarized forms of **4**, the negative charge is distributed between N-9 (**4b**), N-1, and N-3 (**4c**) (Scheme IV). Here attack at C-6 is preferred over C-2 for the following reasons: (a) the vicinity of the positive charge at N-7, (b) concentration of the negative charge in **4c** near position 2. Again we assume that the unequal distribution of negative charge is enhanced by the approach of the nucleophilic reagent.

The polarized forms of the 9-methyl derivative **5** indicate again a higher negative charge around C-2 than C-6 (Scheme III).

Similar reasoning can explain the sequence of hydrolysis in the anions of di- and trichloropurines. In the anion of TCP (**27**), the negative charge is distributed over the imidazole ring (**27a**), N-1, and N-3 (**27b**) (Scheme V). It is evident that only in **27a** is the aromatic structure of the molecule preserved and that the density of negative charge around C-6 is lower than in the vicinity of C-2. This explains the order of reactivity established for TCP[4,5] and similarly for 2,6-dichloropurine (**24**)[3] and its 6,8- (**25**)[8,9] and 2,8-dichloro isomers (**26**).[9] It should, however, be recalled that the absence of an *N*-methyl substituent and the concomitant lack of a positive center in these molecules

SCHEME V



a b

24, $R^1 = R^2 = Cl$; $R^3 = H$
25, $R^1 = H$; $R^2 = R^3 = Cl_2$
26, $R^1 = R^3 = Cl$; $R^2 = H$
27, $R^1 = R^2 = R^3 = Cl$

makes attack of OH^- much more difficult. Thus Fisher[14] isolated crystalline salts of TCP with various metal cations; 6,8- and 2,8-dichloropurine required boiling 4 *N* NaOH to effect hydrolysis.[9]

In summary, the order of reactivity in methylthiopurines, and by analogy in chloropurines, can be explained qualitatively by the combined influence of three factors: (a) the polarity of the molecule, imposed by the presence of an *N*-methyl substituent; (b) the polarizability of the molecule, which enhances small differences in charge distribution during the approach of a nucleophilic reagent; and (c) the preference for resonance forms which preserve the aromatic character of the ring system.

Evidence for the Structure of the Oxopurines, Resulting from Hydrolysis of Methylthio Groups.—Compounds **15**[15] and **18**[16] were identical with known synthetic products. 7-Methyl-2-methylthiohypoxanthine (**23**) was synthesised independently by S-alkylation of the known 7-methyl-2-thioxanthine (**28**)[13] (see Scheme IV). Similarly, 3-methyl-6,8-dimethylthio-2-oxopurine (**19**) was prepared by methylation of 3-methyl-6,8-dithiouric acid (**29**) (see Experimental Section).

Identification of 1-methyl-8-methylthio-2-oxopurine (**17**) is based on the fact that the δ value of the 1-methyl group is shifted upfield by about 0.5 ppm upon hydrolysis of **7** (Table III). On the other hand, the 1-

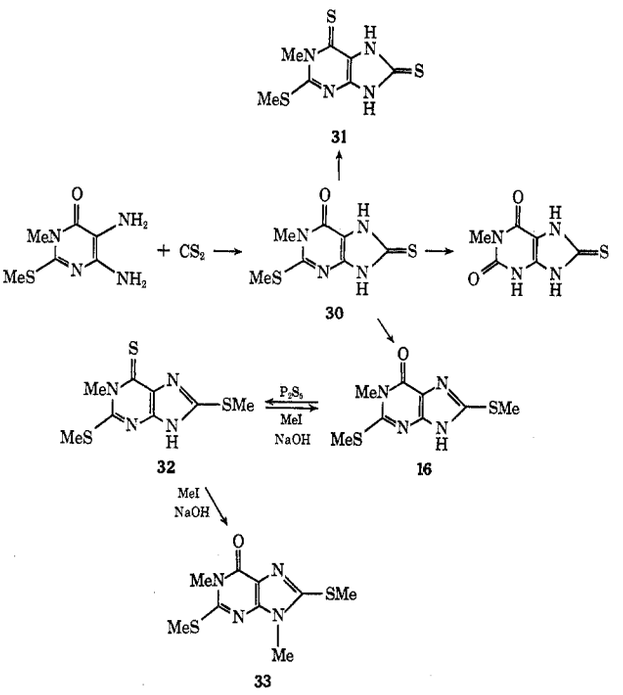
TABLE III
INFLUENCE OF OXO GROUPS ON THE CHEMICAL SHIFT OF THE 1-METHYL GROUP IN PURINES

Registry no.	Compd	δ_{NMe}, ppm, of neutral molecule
21802-40-4	1-Methylpurine	4.20
1008-40-8	1-Methyl-6-methylthiopurine	4.12
1125-39-9	1-Methylhypoxanthine	3.65
39008-42-9	1-Methyl-8-oxopurine	4.19
	1-Methyl-2,6-dimethylthiopurine (**2**)	4.10
38759-23-8	1-Methyl-6-methylthio-2-oxopurine	3.69
39008-44-1	1-Methyl-8-methylthio-2-oxopurine	3.61
39008-45-2	1-Methyl-6-methylthio-8-oxopurine	4.21
	1-Methyl-2-methylthiohypoxanthine (**15**)	3.46
	1-Methyl-2,8-dimethylthiopurine (**7**)	4.06
	1-Methyl-2,8-dimethylthiohypoxanthine (**16**)	3.65
	1-Methyl-8-methylthio-2-oxopurine (**17**)	3.60

methyl signal is displaced only slightly by introduction of an oxo group into position 8. This is seen clearly in Table III by comparison of 1-methylpurine with 1-methyl-8-oxopurine and of other series of 1-methylpurines.

1-Methyl-2,8-dimethylthiohypoxanthine (**16**) was synthesized from 1-methyl-2-methylthio-6-oxo-8-thiopurine (**30**), as shown in Scheme VI.

SCHEME VI



The structure of 9-methyl-2-methylthiohypoxanthine (**21**) is derived from the fact that this compound differs from the alternative product of hydrolysis of **5**, *viz.*, 9-methyl-6-methylthio-2-oxopurine, which has been described recently.[17]

Finally, the structure of 9-methyl-2,6-dimethylthio-8-oxopurine (**22**) was established by elementary analysis, by uv and nmr spectra, and by the fact that this compound differed from the other two possible products of hydrolysis of **14**, *viz.*, 9-methyl-2,8-dimethylthiohypoxanthine (**34**) and 9-methyl-6,8-dimethylthio-2-oxopurine (**36**), which both were obtained by unequivocal procedures (see Table IV and V and Experimental Section).

Experimental Section

All melting points were determined on a Fisher-Johns apparatus and are uncorrected. Analyses were by M. Goldstein, Jerusalem. Uv spectra were measured on a Hitachi Perkin-Elmer Model 124 spectrophotometer and nmr spectra on a Jeol MH-100 instrument, using TSP (sodium 3-trimethylsilylpropionate-*2,2,3,3-d*$_4$ of Merck, Sharp and Dohme, Canada) as internal standard.

For descending chromatography on Whatman paper No. 1, the following solvents were used: A, 1-butanol–acetic acid–water (12:3:5, v/v); B, ethanol–DMF–water (3:1:1, v/v). Spots were located by their fluorescence under a Mineralight UV lamp ($\lambda \sim 254$ nm).

General Procedures. S-Methylation of thiopurines was carried out at room temperature by stirring a solution of the substrate in 1 *N* NaOH with 2 equiv of methyl iodide. The product was precipitated by neutralization with glacial acetic acid.

Hydrolysis of Methylthiopurines. Method A.—A suspension of the substrate in water was refluxed until all the material had gone into solution. The product crystallized upon cooling.

Method B.—A solution of the methylthio derivative in 25% ammonia was kept at room temperature for 10 min.

Method C.—A suspension of the substrate in $NaHCO_3$ was stirred and refluxed for 2 hr. The solution was brought to pH 6 by addition of glacial acetic acid and the precipitate was purified.

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TABLE IV

NEW OXO- AND THIOPURINES

Compd	No.	Mp, °C	Procedure	λ_{max}, nm (log ϵ_{max}), at pH 1	λ_{max}, nm (log ϵ_{max}), at pH 6	λ_{max}, nm (log ϵ_{max}), at pH 12	Solvent for crystn	Crystal form and color	R_f A	R_f B	Fluorescence
A. 1-Methyl Derivatives											
1-Methyl-8-methylthio-2-oxopurine	**17**	>300	From **7**	346 (4.45)	330 (4.04)	286 (4.06) 330 (4.06)	Ethanol	Colorless prisms	0.61	0.51	Bright violet
1-Methyl-2-methylthio-6-oxo-8-thiopurine	**30**	>300	See Scheme VI		253[a] 296				0.7	0.75	Dark violet
1-Methyl-6,8-dithio-2-methylthiopurine	**31**	>300	From **30**		279[a] 369		NaOH–acetic acid	Yellow microcrystals	0.62	0.68	Dark violet
1-Methyl-2,8-dimethylthiohypoxanthine	**16**	275	From **12** and **30**	225 (4.40) 283 (4.47)	280 (4.39)	235 (4.40) 286 (4.36)	Ethanol	Colorless prisms	0.85	0.75	Dark violet
1-Methyl-2,8-dimethylthio-6-thiopurine	**32**	295	From **31**		263[b] 350		Benzene	Yellow needles	0.78	0.73	Dark violet
B. 3-Methyl Derivatives											
3-Methyl-6,8-dithiouric acid	**29**	>300	See Experimental		289[c] 392		NaOH–acetic acid	Yellow microcrystals	0.43	0.71	Brown
3-Methyl-6,8-dimethylthio-2-oxopurine	**19**	268–270	From **29** and **13**	279 (4.04) 370 (4.59)	342 (4.47)	340 (4.45)	Ethanol	Colorless needles	0.84	0.75	Bright violet
C. 7-Methyl Derivatives											
7-Methyl-2-methylthiohypoxanthine	**23**	>300	From **27**	266 (4.27)	225 (4.12) 265 (4.22)	233 (4.45) 274.5 (4.15)	H_2O	Colorless prisms	0.74	0.73	Dark violet
D. 9-Methyl Derivatives											
9-Methyl-6,8-dithiouric acid	**35**	>300	See Experimental	269 307 377	264 309 371		Ammonia–acetic acid	Yellow microcrystals	0.23	0.68	Brown
9-Methyl-2-methylthiohypoxanthine	**21**	>300	From **5**	266 (4.32)	263 (4.20)	272.5 (4.20)	H_2O	Colorless prisms	0.76	0.75	Dark violet
9-Methyl-2,6-dimethylthio-8-oxopurine	**22**	274–275	From **14**	255 (4.25) 316 (4.06)	256 (4.19) 315 (4.09)	286 (4.04) 324 (4.02)	Ethanol	Colorless needles	0.85	0.77	Bright violet
9-Methyl-2,8-dimethylthiohypoxanthine	**34**	>300	See Experimental	283 (4.20)	280 (4.21)	286 (4.24)	1-Butanol	Colorless plates			
9-Methyl-6,8-dimethylthio-2-oxopurine	**36**	276–277	From **35**	248 (4.41) 357 (4.30)	330 (4.28)	327 (4.34)	Ethanol	Colorless rods	0.78	0.71	Greenish blue

[a] Measured only at pH 8.0. [b] Because of the lack of material, the spectrum was measured only in methanol. [c] Measured only at pH 7.0.

TABLE V

No.	Formula	Molecular weight	Analysis, % Calcd C	H	N	S	Found C	H	N	S
17	$C_7H_8N_4OS$	196	42.9	4.1	28.6	16.3	42.7	4.0	28.5	16.2
21	$C_7H_8N_4OS$	196	42.9	4.1	28.6	16.3	42.5	3.9	28.2	16.0
23	$C_7H_8N_4OS$	196	42.9	4.1	28.6	16.3	42.9	4.0	28.3	16.1
29	$C_6H_6N_4OS_2$	214	33.6	2.8	26.2	29.9	33.3	2.6	25.9	29.4
35	$C_6H_6N_4OS_2$	214	33.6	2.8	26.2	29.9	33.2	2.7	25.9	29.5
16	$C_8H_{16}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.6	4.1	23.0	26.3
19	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.5	4.1	23.0	26.2
22	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.4	4.0	23.1	26.3
34	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.4	4.2	22.9	26.1
36	$C_8H_{10}N_4OS_2$	242	39.7	4.1	23.1	26.4	39.2	3.9	22.7	26.0
31	$C_7H_8N_4S_3$	244	34.4	3.3	23.0	39.3	34.2	3.1	22.6	38.8
32	$C_8H_{10}N_4S_3$	258[a]	37.2	3.9	21.7	37.2	37.7	4.1	22.1	36.8

[a] Measured by mass spectrum; nmr ($CDCl_3$) δ 2.76 (s, 2-SMe), 2.84 (s, 8-SMe), 4.16 (s, 1-NMe) ppm.

Method D.—A suspension of the methylthiopurine in 2 *N* NaOH was refluxed for 20 min. The clear solution was brought to pH 6 by addition of glacial acetic acid.

Method E.—A suspension of the substrate in a mixture of 2 *N* NaOH–methanol (4:1) was stirred and refluxed for 30 min. The methanol was removed *in vacuo* and the clear aqueous solution was acidified with glacial acetic acid.

Purines.—The following compounds were prepared according to known procedures: 2,6-dimethylthiopurine (**1**)[18] and its 7-methyl derivative **4**;[13] the other *N*-methyl derivatives of **1**, *viz.*, **2**, **3**, and **5**;[19] 2,8-dimethylthiopurine (**6**)[20,21] and its 1-methyl derivative **7**;[19] 6,8-dimethylthiopurine (**8**),[8] its 3-methyl derivative,[19] and **9** and **10**;[10] 2,6,8-trimethylthiopurine (**11**)[21] and its methyl derivatives **13** and **14**;[19] 1-methyl-2-methylthiohypoxanthine (**15**)[16] and 3-methyl-6-methylthio-2-oxopurine (**18**).[16]

New Compounds. 1-Methyl-2,8-dimethylthiohypoxanthine (16) and Derivatives. A. 1-Methyl-2-methylthio-6-oxo-8-thiopurine (30; See Scheme VI).—A solution of 4,5-diamino-1-methyl-2-methylthio-6-oxopyrimidine[15] (3 g) in pyridine (120 ml) and carbon disulfide (10 ml) was refluxed for 5 hr. The residue, remaining after evaporation of the volatile components, was stirred and heated with water (100 ml) for 10 min. The insoluble brown portion was filtered off and dissolved in 1 *N* NaOH, and the reaction product was precipitated by glacial acetic acid, mp >300° dec (3 g, 82%) (for physical properties see Table IV). Although this compound was not easily purified, its structure was established by hydrolysis with 6 *N* HCl to 1-methyl-8-thiouric acid[22] (see Scheme VI).

B. 1-Methyl-2,8-dimethylthiohypoxanthine (16).—A solution of **30** (1 g) in DMF (50 ml) and methyl iodide (2 ml) was kept at room temperature for 12 hr. The solvent was removed *in vacuo* and the residue was treated with a small amount of cold water. The insoluble portion was dissolved in 1 *N* NaOH and the product was precipitated by neutralization with glacial acetic acid, mp 275°. The compound was identical in all respects with purine **16**, described below (see also Table IV).

C. 1-Methyl-2-methylthio-6,8-dithiopurine (31).—A solution of **30** (3 g) in β-picoline (150 ml) was stirred with phosphorus pentasulfide (6 g) and refluxed for 6 hr. The solvent was evaporated *in vacuo* and the residue was heated with water (250 ml) for 15 min. The insoluble portion was purified, as described under A, as yellow microcrystals (3 g, 93%), mp >300° dec. For physical properties and analysis see Table IV.

D. 1-Methyl-2,8-dimethylthio-6-thiopurine (32).—A solution of the dithio derivative **31** (2 g) in DMF (50 ml) and methyl iodide (5 ml) was kept at room temperature for 12 hr. The solvent was distilled off *in vacuo*, the residue was dissolved in 1 *N* NaOH, and the product was precipitated by addition of glacial acetic acid. From ethyl acetate were obtained yellow needles, mp 295° (1 g, 47%) (see Table IV).

The 6-thio group was not methylated even in boiling DMF. When either **31** or **32** were dissolved in sodium hydroxide and treated at room temperature with methyl iodide, a mixture of two products was obtained. The substance, separating directly from the reaction mixture, was identified as 1,9-dimethyl-2,8-dimethylthiohypoxanthine (**33**).[22] Acidification of the filtrate yielded **16**, identical with the product described under B.

3-Methyl-6,8-dimethylthio-2-oxopurine (19). A. 3-Methyl-6,8-dithiouric Acid (29).—A solution of 4,5-diamino-3-methyl-6-thiouracil (**23**) (21 g) in pyridine (170 ml) and carbon disulfide (21 ml) was stirred and refluxed for 5 hr in the presence of powdered sodium hydroxide (2 g). The solvent was removed *in vacuo* and the residue was dissolved in 2 *N* NaOH. After decolorization with charcoal, the filtrate was brought first to exactly pH 7 with hydrochloric acid and then to pH 6 by addition of acetic acid. The precipitate was purified by repetition of this method as yellow microcrystals (15 g, 57%), mp >300° dec (see Table IV).

B. 3-Methyl-6,8-dimethylthio-2-oxopurine (19).—A solution of the foregoing product (1 g) in 2 *N* NaOH was methylated according to the method described under General Procedures (see Table IV).

7-Methyl-2-methylthiohypoxanthine (23).—**23** was prepared by methylation of 7-methyl-2-thioxanthine (**28**),[18] using the general procedure described above, mp >300° (see Table IV).

9-Methyl-2,8-dimethylthiohypoxanthine (34).—A solution of 9-methyl-2,8-dithiouric acid[19] (1 g) in 2 *N* NaOH (150 ml) was stirred with methyl iodide (2 ml) at room temperature for 1 hr. The precipitate, formed upon neutralization, crystallized from 1-butanol as colorless plates, mp >300° (see Table IV).

9-Methyl-6,8-dimethylthio-2-oxopurine (36). A. Synthesis of 9-Methyl-6,8-dithiouric Acid (35).—A mixture of 9-methyl-8-thiouric acid[23] (5 g), phosphorus pentasulfide (10 g), and pyridine (300 ml) was stirred and refluxed for 4 hr. The solvent was removed *in vacuo* and the residue was treated with boiling water (250 ml) for 15 min. The insoluble portion was dissolved in 25% ammonia (charcoal) and the product was precipitated by neutralization with glacial acetic acid as yellow microcrystals (3 g, 56%), mp >300° dec (see Table IV).

B. 9-Methyl-6,8-dimethylthio-2-oxopurine (36).—Methylation of an alkaline solution of the foregoing product with methyl iodide was carried out as described before; colorless rods (ethanol) (90%) were obtained, mp 276–277° (see Table IV).

Calculation of Superdelocalizabilities.—The Hückel topological matrices were constructed, using the appropriate parametrization of the Coulomb and resonance integrals. After diagonalization (Jacobi's method), the wave functions and energies were subjected to a "frontier" calculation according to the formulation of Fukui.[12] All computations were performed on a CDC 6400 digital computing machine using a Fortran program.

Registry No.—**1**, 39008-18-9; **2**, 39008-19-0; **3**, 39008-20-3; **4**, 39008-21-4; **5**, 39008-22-5; **6**, 39008-23-6; **7**, 39008-24-7; **8**, 39008-23-6; **9**, 18019-39-1; **10**, 18019-41-5; **11**, 39013-71-3; **12**, 39013-72-4; **13**, 39013-73-5; **14**, 39013-74-6; **15**, 33867-98-0; **16**, 39013-76-8; **17**, 39008-44-1; **19**, 39013-78-0; **21**, 39013-79-1; **22**, 39057-19-7; **23**, 39013-80-4; **28**, 39013-81-5; **29**, 39013-82-6; **30**, 39013-83-7; **31**,

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39013-84-8; **32**, 39008-25-8; **34**, 39062-23-2; **35**, 39008-26-9; **36**, 39008-27-0; 4,5-diamino-1-methyl-2-methylthio-6-oxopyrimidine, 39008-28-1; carbon disulfide, 75-15-0; 9-methyl-2,8-dithiouric acid, 39008-29-2; 9-methyl-8-thiouric acid, 39008-30-5; 3-methyl-6,8-dimethylthiopurine, 39008-31-6; 7-methyl-2,6,8-trimethylthiopurine, 39008-32-7.

Acknowledgment.—The authors wish to thank Mr. R. Knafo for the drawings of the schemes.

Pteridines. I. β-Keto Sulfoxides and α-Keto Aldehyde Hemithioacetals as Pteridine Precursors. A New Selective Synthesis of 6- and 7-Substituted Pteridines[1]

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Received January 11, 1973

Alkyl and aralkyl β-keto sulfoxides are converted into 2-amino-4-hydroxypteridines on treatment with 2,4,5-triamino-6-hydroxypyrimidine sulfate and sodium acetate in glacial acetic acid at room temperature for 0.5–1.0 hr followed by refluxing for 1 hr. The only pteridines isolated under these specific conditions are the 6 isomers, with no 7 isomers detected by uv or nmr analysis. In order to account for the positional selectivity of the reaction, a mechanism is proposed wherein β-keto sulfoxides are viewed as "latent" α-keto aldehydes. A regiospecific synthesis of the isomeric 7-substituted pteridines is also described, involving the use of α-keto aldehyde hemithioacetals. Nmr spectra of the 6- and 7-substituted pteridines in FSO_3H and in 1:4 FSO_3H-CF_3CO_2H solution are reported.

The problem of devising a direct and unequivocal route to 6-substituted pteridines has long challenged the imagination of synthetic organic chemists.[2] In the classical approach, condensation of α-keto aldehydes with 4,5-diaminopyrimidines leads to varying mixtures of 6- and 7-substituted products, even in the presence of "aldehyde-protecting" reagents such as sodium bisulfite,[3,4] hydrazine,[5,6] or 2-mercaptoethanol.[7] Similarly, α-keto aldehyde derivatives with the aldehyde function blocked in the form of an acetal[8] or hydrazone[8] afford mixtures because acid-catalyzed partial dissociation to the free aldehyde cannot be completely prevented.[6] Although several alternatives have been developed in order to circumvent these difficulties, they all involve lengthy and sometimes inefficient reaction schemes. Familiar examples include several variants[9,10] of the homofolic and bishomofolic acid synthesis,[11] and also the ingenious pyrazine route devised recently by Taylor and coworkers.[12] This report describes a new pteridine synthesis which is notable for its simplicity and appears to proceed with remarkable positional selectivity. The key element in our approach was the novel use of β-keto sulfoxides,[13] a readily accessible class of compounds whose acid-catalyzed transformations[14,15] allow them to be viewed as "latent" α-keto aldehydes.[16,17]

A representative group of β-keto sulfoxides (**1a–f**), obtained from the appropriate esters *via* the dimethyl sulfoxide–sodium hydride procedure,[13,15] was allowed to react with 2,4,5-triamino-6-hydroxypyrimidine. In every instance the pteridine products were identified as 6-substituted derivatives (**2a–f**), with no evidence for the formation of 7 isomers.

In accord with considerations of a possible mechanism (see Chart I), the reaction was conducted in two stages. After equimolar amounts of each β-keto sulfoxide and of the pyrimidine (in the form of its sulfate salt) were suspended in glacial acetic acid containing 2 molar equiv of sodium acetate, the heterogeneous mixture was

(1) This investigation was supported in part by Research Contract DADA-17-71-C-1001 from the U. S. Army Research and Development Command, Office of the Surgeon General, and by Research Grant C6516 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. This is publication no. 1065 from the U. S. Army Research Program on Malaria.

(2) For a review of recent advances, see "Chemistry and Biology of Pteridines, Proceedings of the Fourth International Symposium on Pteridines, Toba, July 1969," K. Iwai, Ed., International Academic Printing Co., Tokyo, Japan, 1970.

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(17) Following the completion of this work an interesting example illustrating the use of a β-keto sulfoxide as a "latent" α-keto aldehyde appeared; see M. von Strandtman, D. Connor, and J. Shavel, Jr., *J. Heterocycl. Chem.*, **9**, 175 (1972).